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Cerebral haemodynamics, cognition and brain volumes in patients with type 2 diabetes

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with cognitive impairment and brain abnormalities on MRI. The underlying mechanisms are unclear. We examined the relationship between cerebral haemodynamics (cerebral blood flow (CBF) and cerebrovascular reactivity (CVR)) and cognitive performance and brain volumes in patients with T2DM, at baseline and after four years.
Methods: 114 patients with T2DM, aged 56–80 years, underwent a detailed cognitive assessment and MRI scan. In 68 patients the evaluation was repeated after four years. CBF (two-dimensional flow-encoded phase-contrast MRI) and CVR (carbogen breathing response middle cerebral artery; transcranial Doppler) were measured at baseline. Cognitive performance was expressed as composite z-score and regression based index score. Brain volumes were measured on MRI by automated segmentation. The relationship of haemodynamics with cognition and brain volumes was examined with linear regression analyses adjusted for age, sex and IQ.
Results: Mean CVR was 51.8% ± 18.0% and mean rCBF 53.3 ± 11.3 ml/min/100 ml brain tissue. CBF was associated with baseline cognitive performance (standardized regression coefficient β (95% CI): 0.17 (0.00; 0.32) and total brain volume (0.23 (0.05; 0.41)). No correlation was found between CVR and baseline cognitive performance. Neither CBF nor CVR predicted change in cognition (CBF 0.11 (−0.21; 0.44); CVR 0.07 (−0.21; 0.36)) or total brain volume (CBF 0.09 (−0.22; 0.39); CVR 0.13 (−0.13; 0.40)) over four years.
Conclusions: CBF was associated with impaired cognition and total brain volume in cross-sectional analyses, but did not predict changes in cognition or brain volumes over time. Apparently, alterations in cerebral haemodynamics play no major etiological role in cognitive decline or change in brain volumes in non-demented individuals with T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction and an increased risk of dementia (Biessels, Deary, & Ryan, 2008). On brain MRI this is accompanied by modest atrophy and a higher white matter hyperintensity (WMH) load (Biessels et al., 2008; Manschot et al., 2007). We have previously reported that T2DM-related cognitive changes and cerebral atrophy develop slowly over the course of years, at an average rate that is still within the range of that of normal aging (de Bresser et al., 2010; van den Berg et al., 2010). Nevertheless, people with T2DM are overrepresented among those older individuals with accelerated cognitive decline (Reijmer, van den Berg, Ruis, Kappelle, & Biessels, 2010). There is still uncertainty on the etiology, but vascular disease is likely to play a role (Biessels et al., 2008). Indeed clinically manifest atherosclerosis is associated with cognitive impairment in people with T2DM (Bruce et al., 2008; Manschot et al., 2007). Moreover, alterations in cerebral haemodynamics might affect the brain, also in people without clinically manifest cerebrovascular disease. In a cross-sectional study, we observed that cerebral blood flow (CBF) was related to cognition, but there were no differences in CBF between controls and patients with T2DM (Tiehuis et al., 2008). In the present longitudinal study, we further examined the relationship between cerebral haemodynamics, as reflected by CBF and cerebrovascular reactivity (CVR), and cognitive functioning and brain volumes on MRI in patients with T2DM. This relationship was assessed both at baseline and after four years of follow-up.

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2. Methods

2.1. Participants

Participants were included in the Utrecht Diabetic Encephalopathy Study (UDES), a study on determinants of impaired cognition in patients with T2DM. At baseline (2002–2004), 122 patients with T2DM were recruited through their general practitioners. Furthermore, 56 age, sex and IQ matched controls were recruited among spouses and acquaintances of the patients (Manschot et al., 2007). At inclusion, all participants were between 56 and 80 years of age, functionally independent and Dutch speaking. Diabetes duration had to be at least one year. Exclusion criteria were a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning, a history of alcohol or substance abuse or dementia, and a fasting blood glucose $\geq$7.0 mmol/l for control participants. Participants with a history of transient ischaemic attacks or non-disabling stroke could be included.

At follow-up four years later (2006–2008), seven participants had died, four could not be contacted and 59 were not willing or able to participate. Reasons for not participating were: lack of interest ($n=28$); comorbidity ($n=22$; three reported dementia (two patients, one control); and other reasons ($n=9$). One patient with T2DM was excluded because of severe comorbid disease and one control participant fulfilled the criteria for T2DM and was therefore excluded from the control group. Hence, 106 subjects (68 patients and 38 controls) participated in the follow up examination (van den Berg et al., 2010). Baseline characteristics (demographics, cognitive functioning and brain volumes) in participants ($n=106$) and non-participants ($n=70$) at follow-up were similar (for details see (de Bresser et al., 2010) and (van den Berg et al., 2010)). From 43 of the 70 non-participants at follow-up who were alive and could be contacted a cognitive screening test was obtained by telephone (the Dutch version of the Telephone Interview for Cognitive Status (Kempen, Meier, Bouwens, van Deursen, & Verhey, 2007)). Mean performance of non-participants (mean score 35.4$\pm$5.2) was similar to the participants (36.5$\pm$4.6) at follow-up (van den Berg et al., 2010).

The present study only concerns those patients with T2DM from whom baseline CBF or CVR data were available ($n=114$). Data from the control group served as reference values.

The study was approved by the medical ethics committee of the University Medical Center Utrecht and all participants signed an informed consent form.

2.2. Haemodynamics

Both CBF and CVR were measured at baseline. For CBF measurements a 2D-Phase Contrast MR section was positioned at the level of the skull base to measure volume flow in the internal carotid arteries and basilar artery (TR 16 ms; TE 9 ms; flip angle 7.5°; voxel size 0.98x0.98x5.00 mm^3, averages 8; velocity sensitivity 100 cm/s) (Spilt et al., 2002). Total CBF was defined as the sum of flow in both internal carotid arteries and basilar artery. Because total CBF is related to brain size, we calculated relative total CBF (rCBF), expressed as ml/min per 100 ml brain tissue (Appelman et al., 2008).

CVR was assessed with transcranial Doppler (TCD) as described previously.(van Oers, Manschot, van Huffelen, Kappelle, & Biessels, 2006) CVR in response to a rise in CO_2 was determined as the relative change in blood flow velocity in both middle cerebral arteries after 1.5 min of carbogen inhalation. Left and right CVRs were averaged.

2.3. Neuropsychological examination

Neuropsychological examination consisted of 11 tasks, covering 5 cognitive domains (i.e. attention and executive functions, information processing speed, memory, abstract reasoning, and visuoconstruction) (van den Berg et al., 2010). A division in these cognitive domains was made a priori, according to standard neuropsychological practise and cognitive theory (Lezak, Howieson, & Loring, 2004). For the present study we used a composite z-score of tests addressing the first three domains, because these are particularly sensitive to the effects of T2DM and vascular disease (van den Berg et al., 2010). These domains were assessed with the following tests: 1) *attention and executive functions*: Trail-making Test (Part B), Stroop Color–Word Test (Part 3), Brixton Spatial Anticipation Test, a letter fluency test using the 'N' and 'A' and category fluency (animal naming); 2) *information processing speed*: Trail-making Test (Part A), Stroop Color–Word Test (Part 1 and 2), subtest Digit Symbol of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-3); 3) *memory:* forward and backward digit span of the WAIS-3, Corsi Block-tapping Task, Rey Auditory Verbal Learning Test, Location Learning Test, delayed trial of the modified Taylor Complex Figure (Manschot et al., 2006).

Raw test scores at baseline and follow-up were standardized into z-scores per test, by using the pooled mean of baseline scores of the whole group. The z-scores of each domain were calculated by averaging the test scores comprising that domain; these z-scores were averaged to obtain one composite z-score. In secondary analyses, each cognitive domain was addressed separately.

Change in cognitive performance over time was expressed as a regression based index (RBI) score, using the control group as a reference, taking age, sex and estimated IQ into account (Temkin, Heaton, Grant, & Dikmen, 1999). A negative RBI score reflects greater cognitive decline than expected from a control participant with a similar demographic profile and cognitive performance at baseline. The RBI score is preferred over using change in z-scores over time, because it reduces confounding by learning effects and regression to the mean (Temkin et al., 1999). Mean change in performance across the three domains was expressed as a composite RBI score. In secondary analyses, the RBI score of each cognitive domain was addressed separately. Pre-morbid IQ was assessed by the Dutch version of the National Adult Reading test (Manschot et al., 2006).

2.4. Brain volume measurements

MRI scans were acquired on a 1.5 T Philips MR scanner using a standardized protocol (38 contiguous slices, voxel size: 0.9 $\times$ 0.9 $\times$ 4.0 mm^3) and consisted of an axial T1 (repetition time in ms (TR)/ echo time in ms (TE): 234/2), T2 (TR/TE: 2200/100), proton density (TR/TE: 2200/11), inversion recovery (IR) (TR/TE/inversion time in ms (TI): 2919/22/410) and fluid attenuated inversion recovery (FLAIR) (TR/TE/TI: 6000/100/2000) (de Bresser et al., 2010).

After registration of all sequences to the FLAIR image and an inhomogeneity correction, a baseline brain mask was created by a k-means clustering algorithm with 8 clusters for every patient using all sequences. The baseline FLAIR image was rigidly registered to the follow-up FLAIR image within patients. The resulting transform parameters were applied to the baseline mask to create follow-up masks. The uncorrected FLAIR images were multiplied voxelwise times the mask images followed by an inhomogeneity correction. The IR and FLAIR images were used for a k-nearest neighbour-based probabilistic segmentation algorithm that measured total brain, lateral ventricular and WMH volumes on both time points (Anbeek, Vincken, van Bochove, van Osch, & van der Grond, 2005; de Bresser et al., 2010). Volumes were expressed as percentage of total intracranial volume to correct for between subject differences in head size. Volume changes between baseline and follow-up scans were calculated within participants.

2.5. Markers of atherosclerosis

At baseline, carotid intima–media thickness (IMT) was measured in both carotid arteries in a 1-cm trajectory proximal to the beginning of the dilatation of the carotid bulb in 3 different longitudinal projections. IMT was calculated as the mean of these 6 measurements as described previously (Olijhoek et al., 2004).

A history of cardiovascular events was defined as a clinical history of myocardial infarction, stroke (not including TIA) or endovascular or surgical treatment of carotid, coronal or peripheral arterial disease.

2.6. Statistical analysis

Baseline WMH volume was multiplied by 100 and natural-log-transformed because of non-normal distribution (Kolmogorov–Smirnov, $p<0.05$). The relationship between baseline markers of haemodynamics (rCBF, CVR) and baseline or change over time of cognition and brain volumes was examined within the T2DM group with linear regression analyses adjusted for age and sex (cognition also for IQ). These relationships were expressed as standardized betas.

3. Results

Baseline characteristics of the patients with T2DM are presented in Table 1. Mean CVR was 51.8% ± 18.0% and mean rCBF 53.3 ± 11.3 ml/min per 100 ml brain tissue (for the control participants: mean CVR 46.2% ± 16.6% and mean rCBF 57.7 ± 12.2 ml/min per 100 ml brain tissue). At baseline, the patient group with T2DM had a worse cognitive performance than the control group (adjusted mean difference in composite z-score between the T2DM and control group (95% CI) −0.24 (−0.43; −0.05) (For details see (Manschot et al., 2007)). Moreover, patients with T2DM had a significantly smaller relative total relative brain volume (−1.36% of intracranial volume (−2.31; −0.40)) and larger lateral ventricular volume (0.37% (−0.12; 0.87) and WMH volume (0.35 (−0.13; 0.83), WMH volumes were multiplied by 100 and natural-log-transformed) (For details see (de Bresser et al., 2010)).

Table 1
Baseline characteristics.

Patients with type 2 diabetes ($n=114$)	
Sex (men)	59 (52)
Age (years)	65.9 ± 5.8
Estimated IQ	98 ± 15
Diabetes duration (years)	8.7 ± 6.1
HbA1c level (%)	6.8 ± 1.1
Fasting glucose levels (mmol/l)	8.6 ± 2.9
Use of insulin	32 (28)
Smoking (present or past)	78 (68)
Hypertension [a]	62 (54)
Hypercholesterolemia [b]	69 (61)
Cardiovascular event [c]	30 (26)
Stroke	7 (6)
Carotid intima-media thickness (mm) ($n=108$)	0.93 ± 0.17
Cerebrovascular reactivity (%) ($n=96$)	51.8 ± 18.0
Total relative cerebral blood flow (ml/min per 100ml brain tissue) ($n=85$) [d]	53.3 ± 11.3

Data shown are means ± SD or *n*. Values in parenthesis are percentages.
[a] Defined as a systolic blood pressure >160 mmHg or a diastolic pressure >95 mmHg or use of antihypertensive drugs primarily for hypertension.
[b] Defined as a fasting cholesterol >6.2 mmol/l or self reported use of lipid lowering drugs.
[c] Defined as history of a myocardial infarction, stroke (not including TIA) or endovascular treatment of carotid, coronal or peripheral arterial disease.
[d] Defined as the summed flow in both carotid arteries and the basilar artery.

Tables 2 and 3 show the associations of haemodynamics with cognition and brain volumes. At baseline, lower rCBF was associated with a lower composite z-score (β (95% CI): 0.17 (0.00; 0.32), $p=0.046$). In secondary analyses on each cognitive domain separately, lower rCBF was significantly associated with the domains attention and executive functioning (0.19 (0.02; 0.38), $p=0.034$) and information processing speed (0.21 (0.01; 0.42), $p=0.039$). After additional adjustment for a history of stroke, the association between rCBF and composite z-score was attenuated (0.16 (0.00; 0.34), $p=0.053$). In contrast, adjustment for C-IMT (0.17 (0.00; 0.33), $p=0.056$), cardiovascular events (0.19 (0.02; 0.33), $p=0.025$) or both (0.19 (0.02; 0.33), $p=0.027$) did not essentially change the association. Lower rCBF was also significantly associated with lower baseline relative total brain volume (0.23 (0.05; 0.41, $p=0.01$). Adjustment for C-IMT (0.24 (0.05; 0.42), $p=0.01$), cardiovascular events (0.24 (0.07; 0.42) $p=0.01$), a clinical history of stroke (0.22 (0.05; 0.39), $p=0.01$) or all these factors (0.25 (0.06; 0.43) did not change this association. Importantly, in the patients with T2DM who also attended the follow up examination, the same relationship at baseline between CBF and composite cognition (0.25 (0.02; 0.45) and total relative brain volume (0.27 (-—0.02; 0.58) was found. It should be noted that rCBF was expressed in ml/min per 100 ml brain tissue. Hence, in patients with relatively lower brain volume, perfusion per 100 ml brain tissue was even less.

No significant relationships between CVR and baseline composite z-score, relative total relative brain volume, lateral ventricular volume and WMH volume were observed.

Over four years, across the group of patients with T2DM cognitive decline was not accelerated compared to the reference group (composite score: RBI score ± SD −0.06 ± 0.73; mean change in z-score ± SD −0.11 ± 0.24; for details see (van den Berg et al., 2010)). Within the T2DM patient group neither baseline CVR, nor rCBF, was significantly related to cognitive decline over the 4 years of the study (Table 2).

Over the four years, total relative brain volume decreased (change over time (%) ± SD: −1.46 ± 0.71) and lateral ventricular (0.36% ± 0.25%) and WMH volume increased (0.14% ± 0.18%) in the patients with T2DM. Only the increase of lateral ventricular volume was significantly accelerated relative to controls (adjusted difference between T2DM and control group (95% CI): 0.11% (0.00; 0.22)) (for details see (de Bresser et al., 2010)). No significant associations between baseline rCBF or CVR and change of brain volumes over four years were found (Table 3).

4. Discussion

In this study sample of non-demented older patients with T2DM, rCBF was associated with impaired cognition and total brain volume in cross-sectional analyses. However, cerebral haemodynamics at baseline appeared to be no predictor for changes in cognition or brain volumes over time.

There is still uncertainty on the risk factors for cognitive decline and brain abnormalities in T2DM. Previous studies, mostly cross-sectional in design, point to chronic hyperglycaemia and microvascular complications as well as atherosclerosis as relevant factors (Biessels et al., 2008). A recent study found a relationship between atherosclerosis (ankle–brachial index) and incident dementia after six years in older patients with T2DM (Bruce et al., 2008). Likewise, in the general population, atherosclerosis, also in blood vessels not supplying the brain, is associated with cognitive impairments (de la Torre, 2004; Hofman et al., 1997; Mathiesen et al., 2004). In previous papers on the present study population, we reported that in patients with T2DM a history of cardiovascular events was associated with impaired information processing speed and memory, and more severe vascular lesions on MRI (Manschot et al., 2007), but

Table 2
Relationship between baseline haemodynamics in patients with T2DM and cognition at baseline and change in cognition during follow-up.

	Composite cognition	Attention and executive functioning	Information processing speed	Memory
Baseline[a]				
CVR (%) ($n=96$)	0.04 (−0.16; 0.25)	0.02 (−0.12; 0.16)	0.08 (−0.13; 0.30)	−0.03 (−0.15; 0.10)
rCBF (ml min^{-1} 100 ml^{-1}) ($n=85$)	0.17 (0.00; 0.32) [c]	0.19 (0.02; 0.38) [c]	0.21 (0.01; 0.42) [c]	−0.10 (−0.29; 0.10)
Longitudinal change [b]				
CVR (%) ($n=58$)	0.07 (−0.21; 0.36)	0.17 (−0.10; 0.44)	0.03 (−0.22; 0.28)	−0.16 (−0.43; 0.10)
rCBF (ml min^{-1} 100 ml^{-1}) ($n=47$)	0.11 (−0.21; 0.44)	0.16 (−0.16; 0.47)	0.01 (−0.19; 0.20)	0.00 (−0.48; 0.48)

Data are standardized regression Beta-coefficients (95% CI), adjusted for age, sex and IQ.
CVR = cerebrovascular reactivity, rCBF = relative cerebral blood flow.
[a] At baseline cognition is expressed as a (composite) z-score.
[b] The change in cognition over time is expressed as regression based index (RBI) score.
[c] $p<0.05$.

cardiovascular events did not predict cognitive decline over four years (van den Berg et al., 2010), or brain volume changes (de Bresser et al., 2010).

The association between atherosclerosis and cognitive dysfunction and dementia might be mediated by alterations in cerebral haemodynamics. However, inter-individual variation in haemodynamics can obviously also reflect processes other than atherosclerosis. Indeed, in the present study the relationship between rCBF and cognitive dysfunction at baseline was independent of IMT and a history of cardiovascular events. However, this association was not independent of a clinical history of stroke. To the best of our knowledge there are no other published studies on the relation between cerebral haemodynamics and cognition in patients with T2DM. In the general population, rCBF was found to be cross-sectionally associated with cognitive functioning (especially information processing speed and executive functioning). This association was mediated by brain atrophy (Poels et al., 2008) and WMH (Appelman, van der Graaf, Vincken, Mali, & Geerlings, 2010). Furthermore, earlier cross-sectional studies found cerebral hypoperfusion to be associated with cognitive impairment and Alzheimer's disease (Johnson et al., 2005).

Regarding the relationship between cerebral haemodynamics and structural brain MRI markers, previous cross-sectional studies, not specifically addressing T2DM, found reduced rCBF in non-demented older individuals and older people with vascular risk factors to be associated with WMH severity (Bastos-Leite et al., 2008; van Es et al., 2010). However, previous studies on the relation between rCBF and brain atrophy in elderly individuals with vascular risk factors show conflicting results. While one study observed no relationship between rCBF and atrophy (van Es et al., 2010), another study found rCBF to be associated with subcortical atrophy (Appelman et al., 2008). In patients with T2DM, a cross-sectional relationship between lower regional rCBF and brain atrophy has previously been reported (Last et al., 2007), in line with the cross-sectional analyses in the present dataset.

Remarkably, cerebral haemodynamics were unrelated to cognitive decline and progression of atrophy in this sample. This does not support a causal role for disturbed haemodynamics in cognitive dysfunction and atrophy as might be inferred from the cross-sectional studies. Reverse causality might even play a role. In other words, the demand for CBF may be relatively lower in abnormal atrophic brain tissue, thus giving rise to the observed associations in the cross-sectional studies. This does not imply, however, that the impact of T2DM on the brain is independent of vascular disease. In fact, white matter hyperintensities and lacunar infarcts on brain MRI are more common in patients with T2DM and these lesions are associated with cognitive decline and brain atrophy (Sima, 2010). Moreover, recent autopsy studies indicate that vascular brain damage is the key neuropathological determinant of increased dementia risk in T2DM (Ahtiluoto et al., 2010).

Strengths of the present study are the prospective design in combination with detailed assessment of cognitive status and precise brain volume measurements. A limitation is that the sample size was modest. Nevertheless, point estimates for the regression coefficients in the longitudinal data were close to 0, with relatively narrow 95% confidence intervals, indicating that variation in haemodynamics could explain, at most, 5% of the variation (coefficient of determination) in the changes in cognition and brain volumes over four years, and that our negative results are not due to lack of statistical power. Another limitation could be the possible selective loss to follow-up. However, participants and nonparticipants were comparable at baseline (demographics, brain volumes) and follow-up (cognitive status) (de Bresser et al., 2010; van den Berg et al., 2010). Finally, our global measures of CBF and CVR may have missed regional abnormalities.

In summary, the present study showed that CBF was associated with impaired cognition and total brain volume in cross-sectional analyses but neither CBF, nor CVR predicted cognitive decline or change of brain volumes over time. Apparently alterations in cerebral haemodynamics play no major etiological role in cognitive decline or change in brain volumes in non-demented individuals with T2DM.

Table 3
Relationship between baseline haemodynamics in patients with T2DM and brain volumes at baseline and change in brain volumes during follow up.

	Total brain volume (%ICV)	Lateral ventricular volume (%ICV)	WMH volume [a]
Baseline			
CVR (%) ($n=96$)	−0.06 (−0.27; 0.13)	0.20 (−0.03; 0.41)	0.05 (−0.19; 0.26)
rCBF (ml min^{-1} 100 ml^{-1}) ($n=85$)	0.23 (0.05; 0.41) [b]	−0.12 (−0.33; 0.11)	−0.18 (−0.44; 0.00)
Longitudinal change			
CVR (%) ($n=58$)	0.13 (−0.13; 0.40)	0.05 (−0.14; 0.19)	0.14 (−0.14; 0.56)
rCBF (ml min^{-1} 100 ml^{-1}) ($n=47$)	0.09 (−0.22; 0.39)	−0.08 (−0.53; 0.38)	−0.23 (−0.62; 0.08)

Data are standardized regression Beta-coefficients (95% CI), adjusted for age and sex.
WMH = white matter hyperintensities, CVR = cerebrovascular reactivity, rCBF = relative cerebral blood flow, %ICV: percentage of intracranial volume.
[a] Relative baseline WMH volumes were multiplied by 100 and natural-log-transformed.
[b] $p<0.05$.

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